Urology Update from Jackson Hole

Highlights from the 3rd Annual Jackson Hole Summer Urologic Conference
July 28–August 3, 2001, Jackson Hole, WY

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The 3rd annual Summer Jackson Hole Urologic Conference in Jackson Hole, WY once again combined an outstanding educational format with a spectacular venue. Conceived over two decades ago by Ralph Hopkins, a practicing urologist from Riverton, WY, the Jackson Hole meeting combines an internationally recognized faculty with an equally renowned critique panel. The faculty present a series of papers in their areas of expertise and the critique panel is afforded sufficient time to critically analyze and evaluate the presentations. This results in some good-natured ribbing but also allows critical assessment of the data presented.

Reviewed by Michael K. Brawer, MD, Northwest Prostate Institute, Seattle, WA

Prostate Cancer

TURP-Detected Prostate Cancer

Gerald Andriole presented a number of interesting papers, primarily on carcinoma of the prostate, based on his vast experience at Washington University School of Medicine in St. Louis. In a paper on the frequency and histopathologic features of transurethral resection of the prostate (TURP)-detected prostate cancer, he first reviewed the literature on the incidence of transition zone carcinoma (see Table 1).[1–7] He went on to describe his experience in the prospective evaluation of 259 men with lower urinary tract symptoms (LUTS) who underwent TURP. All men with either an abnormality on digital rectal examination or elevated prostate-specific antigen (PSA) underwent at least one set of peripheral and/or transition zone biopsies that were negative for cancer. The incidence of cancer and the number of prior negative biopsies are shown in Table 2. These data demonstrate that a considerable portion of patients who have negative peripheral and indeed transition zone biopsy may harbor significant carcinoma of the prostate at the time of TURP. The decrease in incidence of TURP as we move more and more to pharmacologic and alternative therapies for LUTS owing to presumed benign prostatic hyperplasia (BPH) underscores the need to periodically evaluate those patients for prostate cancer.

Gleason Score 3+4 Versus 4+3

Dr. Andriole reviewed the differences between Gleason 3+4 and Gleason 4+3 in another presentation. He eval-

Table 1
Percent Prostate Cancer in Transition Zone Biopsies if Prior Negative Prostate Biopsy

Repeat Positive Biopsy Rate	Prostate Cancer Only in Transition Zone	Author
37%	–	Lui et al[1]
31%	10%	Liu et al[2]
32%	15%	Babaian[3]
24%	3%	Bazimet et al[4]
16%	10%	Keetch et al[5]
21%	9%	Morote et al[6]
18%	12%	Onder et al[7]

uated 133 men with Gleason 3+4 and 24 men with Gleason 4+3 who were followed for a mean time of 38.6 months. Those men with Gleason 4+3 had the higher pathologic stage and larger tumor volume, although these differences were not statistically significant. The incidence of PSA recurrence for those men with Gleason 4+3 was significantly greater than those with Gleason 3+4 (P = .0008). These data confirm the observation from the Stanford group and others that increasing percentage of Gleason grade 4 and/or 5 connotes an adverse prognostic indication.

Radical Prostatectomy

In a paper addressing the use of selective cavernous nerve resection and sural nerve grafting for men undergoing radical prostatectomy, Dr. Andriole gave a balanced presentation. He noted that, although technically feasible, the indication for wide resection of the nerve vascular bundles is at best obscure. Using preoperative parameters may result in inappropriate nerve resection in 15% to 60% of cases. He concluded that until more is known about the appropriate factors to guide the decision for nerve resection, which hopefully will come from advances in staging methodology, this procedure should be considered investigational.

The finding of positive surgical margins at the time of radical prostatectomy continues to occur all too often, and the appropriate intervention remains obscure. Dr. Andriole identified 33 men with isolated positive apical margins and compared them to a cohort of patients matched by age and preoperative PSA and biopsy Gleason parameters who were shown to have pathological T2 disease. Patients were evaluated for PSA failure at 1-, 3-, and 5-year intervals. PSA recurrence for survival at 5 years was 75% and 77%, respectively, for those with positive and negative apical margins (P > .10). Dr. Andriole concluded that when controlling for other prognostic parameters a positive margin at the apex is not associated with untoward prognosis.

Percent of Positive Biopsies as a Predictor of Outcome

Gary Grossfeld, Assistant Professor of Urology at the University of California at San Francisco, also focused primarily on carcinoma of the prostate. One paper addressed the use of the percent of biopsies with cancer to predict tumor extent and outcome following radical prostatectomy. He used the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) registry of patients throughout the United States. Univariate and multivariate analysis demonstrated that PSA at diagnosis, biopsy Gleason score, and the percentage of positive biopsies (number of positive biopsies/total number of biopsies) all were significant predictors of both extracapsular disease and disease recurrence. The percent of biopsies that revealed carcinoma was the most important predictor for the likelihood of extra prostatic disease and disease recurrence for those patients with intermediate or high-risk disease characteristics, based on clinical tumor stage, serum PSA, and

Table 2
TURP-Detected Prostate Cancer

	No. Patients	No. (%) with Prostate Cancer
No prior biopsy	40	6 (15)
One or more negative peripheral zone biopsy only	105	13 (13)
1 or more negative peripheral + T2 biopsy	144	11 (8)

Data from Ornstein et al.[26]
TURP, transurethral resection of the prostate.

Table 3
Trials Comparing Bicalutamide Monotherapy with Castration

Author	N	Dose	Stage of Disease	Comparison	Result
Chodak et al[9]	486	50 mg	Stage D2	Castration	Longer progression-free with castration
Bales and Chodak[10]	1037	50 mg	Stage D2	Castration	Longer median survival with castration
Tyrrell et al[11]	1453	150 mg	Metastatic and locally advanced	Castration	Longer survival in M1 patients with castration
Boccardo et al[12]	229	150 mg	Metastatic and locally advanced	Combined androgen blockade	No difference in progression-free or overall survival
Iversen et al[8]	480	150 mg	Locally advanced	Castration	No difference in survival

biopsy grade. In a subset of low-risk patients, disease recurrence at 5 years was 15% for those with one third or less of the biopsies positive, as compared to 31% for those that had more positive biopsies. Similar findings were noted with intermediate- and higher-risk disease. The simplicity of simply identifying the number of biopsy cores that are positive renders this approach widely applicable, although certainly not as reproducible as a more sophisticated measurement, such as percent of cancer within a biopsy or millimeters of biopsies that showed carcinomas. Using percent of positive biopsies as a measure obviously has more general appeal. Obviously one confounder is the number of biopsies obtained, and this needs to be standardized for this method to be useful.

Intermittent Androgen Deprivation

Dr. Grossfeld provided an update on the University of California experience with intermittent androgen deprivation. Sixty-one patients were treated, including 34 patients with clinically localized disease and no prior treatment and 27 patients who had recurrent disease following local therapy. In their study, the University of California group treats patients with 6–9 months of androgen deprivation during the initial cycle. They continue this for 1 to 2 months after PSA either reaches a nadir or becomes undetectable. Patients who achieved a PSA nadir less than 0.1 ng/mL (for those with prior definitive local therapy) or less than 4.0 ng/mL (for those with no prior local therapy) are eligible for going off therapy. Androgen deprivation is then reinstituted when serum PSA reaches a predetermined level either greater than 50% of the pretreatment level or greater than 10.0 ng/mL, or by patient request. With follow-up between 7 and 60 months following the start of treatment, with a mean of 30 months, patients received one to five treatment cycles with a median of 2 cycles and the median cycle length being 14 months. Importantly, patients were off androgen deprivation 45% of the time, although this time interval decreased with the increasing number of cycles. Among a small subset of patients in which quality of life was measured with a variety of instruments, the researchers noted clinically significant improvement in health-related quality of life during the off-treatment episodes in the domains of vitality and fatigue, sexual function, and sexual bother.

Anti-Androgen Monotherapy

Dr. Grossfeld reviewed the experience with anti-androgen monotherapy in prostate cancer. A number of studies have reported on the use of bicalutamide in either the 50 or 150 mg per day dosing. These demonstrated that castration was superior irrespective of bicalutamide dose. Iversen and associates[8] observed that in 480 patients with locally advanced nonmetastatic prostate cancer and a median follow-up of 6.3 years, high-dose bicalutamide was reported to be equivalent to castration in terms of time-to-disease progression and overall survival. Significant benefit to the patients randomized to bicalutamide included improvement in sexual interest and physical capacity. Adverse side effects included hot flashes in the castration group and breast pain and gynecomastia in the bicalutamide group. Table 3 depicts several trials in which bicalutamide is compared with surgical or pharmacologic castration.[8–12]

Management of Disease Following Radical Prostatectomy

The management of the man with positive surgical markers following radical prostatectomy is, as noted above, a confusing one. No definitive trials have been reported in which patients were properly randomized. Options include delayed radiation or androgen deprivation at the time of disease progression, immediate adjuvant radiation, or androgen deprivation. Each has its proponents. Grossfeld noted that although immediate radiation therapy in an adjuvant setting is certainly advocated by many, if not most, radiation oncologists, data from the University of Colorado and San Francisco demonstrate that if therapeutic radiation is given with a PSA below 2.0 ng/mL, the results are indistinguishable from patients receiving adjuvant radiation before PSA becomes detectable.[13] Dr. Grossfeld described a decision analysis model to determine the preferred management of positive surgical margins.[14] Using the average probability assessments from the literature, the decision model recommended initial surveillance. Sensitivity analyses demonstrated the model was dependent on the probability of disease recurrence in patients followed expectantly as well as the efficacy of therapeutic radiation.

Urinary Diversion

Dr. Grossfeld gave an interesting talk on orthotopic urinary diversion in women requiring cystectomy. He noted that increase in experience demonstrated that this method is a safe and reliable method of urinary diversion in properly selected patients. Examination must include assurance that urethra is not involved in neoplasia. Stein and associates[15] noted that the only risk factors for urethral involvement, based on 67 female cystectomy specimens, are tumor involvement of the bladder neck or the anterior vaginal wall. Dr. Grossfeld's summary of the literature may be found in Table 4.

Incontinence

Niall Galloway, Associate Professor and Director of the Emory Continence Center in Atlanta, presented a number of papers on pelvic anatomy and the mechanisms of cystocele, rectocele, and urinary incontinence. In an illuminating presentation on the evaluation of the incontinent patient, Dr. Galloway cautioned that although traditional medical specialties have divided the organs of the pelvis into the gastrointestinal, gynecologic, and genital urinary "camps," that in fact these organs work together in health and often fail together in disease. He underscored the need for a broader approach to optimum management of patients with pelvic disorders. In addition to the evaluation of the patient, Dr. Galloway emphasized the importance of a full clinical history, a thorough physical examination, measurement of uroflow and postvoid residual volume, and urine analysis. He has his patients keep a bladder diary before their visit.

One point that was illuminating to most of the audience was that the foot is innervated by S2 and S3, and thus examination of the feet gives an

Table 4
Continence Results for Women Undergoing Orthotopic Urinary Diversion Following Cystectomy

Author	Year	N	% Continent	% Catheterize	% Additional Treatment for Incontinence
Stein (personal communication)	2001	88	75%	34%	14%
Blute and Gburek[27]	1998	5	80%–100%	20%	–
Cancrini et al[28]	1995	7	71%–100%	–	–
Hautman et al[29]	1996	18	85%	70%	–
Jarolim et al[30]	1997	12	92%	8%	–
Mills and Studer[31]	2000	15	80%–100%	7%	–
Shimogaki et al[32]	1999	8	88%	50%	–
Stenzl et al[33]	1997	20	79%–88%	4%	–
UCSF	2001	25	76%	8%	16%

UCSF data from Gary D. Grossfeld, MD.

Table 5
Spontaneous Passage Rates for Ureteral Stones

Size	Rate	Location	Rate
<4 mm	57%	Proximal	12%
4–6 mm	35%	Middle	22%
>6 mm	8%	Distal	45%

Data from Hubner et al.[16]

indication of the neuronal health or lack thereof of the pelvic floor and sphincters, which are innervated by S3, S4, and S5. Another physical finding that may demonstrate underlying pathology is asymmetry of the buttocks and gluteal folds in the standing position. Two-point discrimination, he feels, should be evaluated in the peri-anal and post-anal dermatomes and muscle tone and group of the circum-vaginal and anal sphincter muscles. The perineum should be examined with a full bladder in the standing as well as the supine position. The bladder scan provides an easy method of evaluating a post-void residual volume, which can be measured repeatedly.

Dr. Galloway advocates non-surgical treatments for all patients initially. These include fluid and bowel management, skin care, and containment issues. Careful drug history is important, and agents such as α-blockers should be avoided, as they result in incontinence. Dr. Galloway recommends a natural conservation management and evaluation. However, if the symptoms are moderate or severe, or if anatomical defects are present, urodynamic evaluation is important.

Endourology

Distal Ureteral Stones

Dr. Margaret Pearle, Associate Professor of Urology at the University of Texas Southwestern Medical Center, provided an update on a number of endourologic advances. Perhaps no field of urology is today more controversial than the option of therapy for distal ureteral stones. She noted that observation is appropriate in select cases, and with ureteral stent placement to dilate the ureter, spontaneous passage is common. Ureteroscopy (URS) and shockwave lithotripsy (SWL) are both highly successful with low complication rates. Salvage therapy, either laparoscopic or open ureterolithotomy, are rarely needed. The rates for spontaneous passage of stones have been reviewed by Hubner et al[16] (see Table 5). The use of a stent as definitive management is demonstrated by Leventhal et al.[17] He randomized men to URS versus stent placement. Seventeen patients were initially managed with a ureteral stent. Eighty-three percent passed the stone at a mean of 6.6 days. There was no difference in stone size between groups. Dr. Pearle made the point that when SWL is considered for ureteral stone management, if a stent needs to be passed it may be just as easy to pass a 7 French ureteralscope and treat the stone definitively. Complications associated with SWL are primarily related to fragment passage, with sepsis occurring in 1% to 1.5%. No ureteral injury or stricture has been reported with SWL in the absence of manipulation or stem placement. Complications from URS include a perforation rate that is now less than 4% and late ureteral stricture formation in 2%.

Wollin and Denstedt[18] randomized 58 patients with ureteral stones to receive a stent or not. At 1 week, flank and bladder symptoms were greater in patients with a stent. One hundred percent stone-free status was achieved in all patients, and one patient in each group required an emergency room visit or admission. These authors concluded that routine stent placement after uncomplicated URS for distal ureteral stones may be unnecessary. A number of studies have been reported in which patients were randomized to URS versus SWL for distal ureteral stones. A report by Deliveliotis et al[19] randomized patients equally to URS versus SWL. For distal stones, stone-free rates were 100% in the URS group and 98% in the SWL group, with a 6% retreatment rate. SWL operating room time was 10 minutes shorter, and there was a 4% stricture rate in

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Table 6
Balloon Dilation: Review of the Literature

Author	N	Caliber Balloon	Size Stent (Fr)	Duration of Stent	Success	Follow-up
Johnson et al[34]	31	4–10 mm	5–14	≥2 d	58% (18/31)	≥6 mo
Smith[35]	5	–	–	–	39% (7/18)	–
Chang et al[22]	10	5–8 mm	8–16	4–8 wk	70% (7/10)	–
O'Brien et al[36]	14	4–6 mm	8.5	–	57% (8/14)	14 mo
Beckmann and Roth[37]	17	4–10 mm	7–10	4–8 wk	82% (14/17)	15 mo
Kramolowsky et al[38]	14	–	–	–	64% (9/14)	27 mo
Netto et al[39]	21	4–6 mm	8.5	Average 40 d	57% (12/21)	21 mo
Ravery et al[40]	11	10 mm	8	2.1 mo	40% (4/10)	16 mo
Total	123	–	–	–	59% (79/135)	–

the URS group, with none in the SWL group. Peschel et al[20] reported on 80 patients with distal ureteral stones that failed to pass in 3 weeks. They were randomized to SWL or URS. Stone-free rates were 90% in the SWL and 100% in the URS group. Operating room times were shorter for URS, as was time to becoming stone-free.

Ureteral Strictures

Dr. Pearle reviewed the endourologic management of ureteral strictures. She notes that URS is the most common cause today for these. Treatment options include balloon dilation, endoureterotomy, and ureteroneocystostomy. She reviewed the literature with respect to balloon dilation, as is shown in Table 6. Diagnostic factors associated with stricture duration have been reported by Beckmann[21] for strictures of less than 3 months' duration. There was an 88% success rate, compared to 67% for those of longer status. Chang et al[22] noted 91% success for strictures of less than 3 months versus 25% for those greater than 3 months. Chang[22] also noted the length of stricture would offer prognostic information, with 100% of stricture success with balloon dilation for those less than 1.5 cm versus 12.5% for those greater than 1.5 cm. Endoureterotomy technique was discussed. Dr. Pearle recommends a transmural endoscopic incision through the stricture extending into normal ureter proximally and distally. Stent placement for 6 weeks is required. A review of the literature with respect to endoureterotomy may be found in Table 7. Complications from endoureterotomy include rare urinoma formation and ureteroenteric fistula. Vascular injuries also are rare but must be considered as a potential outcome. Dr. Pearle concluded that endourologic management of benign ureteral and ureteroenteric strictures provides reasonable first-line therapy. Endoureterotomy has a higher success rate than balloon dilation and the

Table 7
Endoureterotomy: Results

Author	N	Modality	Follow-up	Success
Schneider et al[41]	12	Cold knife	15 mo	67% (8/12)
Meretyk et al[42]	13	Electrified cut	20 mo	62% (8/13)
Yamada et al[43]	20	Cold knife	18 mo	85% (17/20)
Cornud et al[44]	31	Electrified cut	>12 mo	71% (22/31)
Preminger et al[45]	40	Acucise	8.7 mo	53% (21/40)
Singal et al[46]	12	Ho:YAG	≥9 mo	75% (9/12)
Wolf et al[47]	38	Variety	28 mo	82% (31/38)
Total	166	–	–	70% (116/166)

latter is exceedingly prone to failure for ureteroenteric strictures. She underscored the need for prospective randomized trials to optimize treatment methods.

Lower Pole Ureteral Stones

Management of the lower pole ureteral stone remains controversial. Perhaps the most important study in this regard was the meta-analysis performed by Lingeman et al.[23] Thirteen shockwave studies and three percutaneous nephrolithotomies were evaluated. This study demonstrated that, controlling for stone size, patients with lower pole stents are 6.27 times more likely to be rendered stone-free with percutaneous approaches as compared to SWL. The prospective randomized trial by Lingeman, in which 160 patients were randomized to SWL versus percutaneous nephrolithotomy (PCNL) and stratified with stone size, demonstrated that lithotripsy resulted in stone-free status in only 37%, compared to 95% of those having a percutaneous approach. Dr. Pearle's algorithm for the management of lower pole stones is shown in Figure 1. Dr. Pearle's conclusion as to the outcome and management of lower pole calculi is that for small stones (<10 mm), SWL is reasonable first-line therapy. For larger stones (>20 mm), PCNL is preferred. For stones intermediate in size (11–20 mm), the main treatment decision is based on renal anatomy and stone composition. She added that ureterorenoscopy is a reasonable option for small to mid-size stones or stones that have failed SWL.

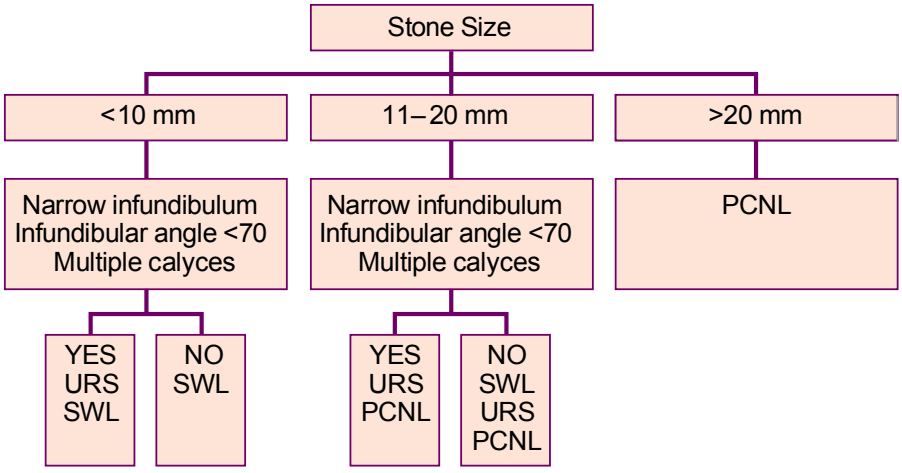

Figure 1. *Algorithm for management of lower pole stones. URS, ureteroscopy; SWL, shockwave lithotripsy; PCNL, percutaneous nephrolithotomy.*

Infertility

Lawrence Ross, Professor and Chairman of the Department of Urology at the University of Illinois, presented a number of papers on the management of infertility. In an informative lecture on the role of testis biopsy in the modern management of infertility, Dr. Ross said there is little role for same. The differential of obstructive versus nonobstructive azoospermia can not be determined by physical examination of the testis and endocrine profiles. In a very interesting paper, Dr. Ross reviewed the cost/benefit analysis of the management of male infertility. He noted that in cases of severe male factors, such as azoospermia and severe oligospermia, the only treatment approach may be in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI). But in the more common, treatable forms of male infertility, including varicocele, obstructive azoospermia, endocrine dysfunction, and infection, definitive therapy of these conditions may be more cost-effective. In a study by Neumann and associates,[24] charges per cycle for IVF from six facilities in the United States and estimated delivery rates from the published literature were evaluated. They observed that the cost per success for delivery with IVF was $66,667 for the first cycle, increasing to $114,286 by the sixth cycle. The cost was considerably greater in older women and if there was a male factor contributing to the

Critique Panel, 3rd Annual Jackson Hole Summer Urologic Conference

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infertility. The Society for Assisted Reproductive Technology has reported that for the most recent reporting period (1998), when three embryos are transferred in an IVF cycle, the live birth rate is 37.7% for a woman 20 to 29 years of age, diminishing to 8.3% for women 40 to 44. The overall birth rate per cycle for all patients undergoing IVF remains at 25% and unfortunately has not changed over the last 5 years.

Schlegel[25] did a cost-effectiveness comparison of varicocele ligation to IVF/ICSI. The cost for varicocelectomy was $26,268 versus $89,091, based on figures from Cornell University. They noted that the average published delivery rate for ICSI was 28% versus 30% for vericocolectomy. Comparing similar results for vasectomy reversal, the cost for delivery was $72,521 for sperm retrieval and ICSI versus $25,475 for vasovasostomy. These data suggested that in cases of male-factor infertility procedures directed to the male generally are more cost effective and allow natural conception.

Upcoming Meetings at Jackson Hole

The 2002 Jackson Hole Summer Meeting will be held July 27–August 2. Interested readers should contact Kay Christensen, Conference Coordinator, for more information at 307-856-5758.

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Main Points

- A prospective evaluation of 259 men with lower urinary tract symptoms (LUTS) who underwent transurethral resection of the prostate (TURP) demonstrated that a considerable portion of patients who have negative peripheral and transition zone biopsy may harbor significant carcinoma of the prostate at the time of TURP.
- A study comparing 33 men with isolated positive apical margins following radical prostatectomy to a cohort of controls concluded that, when controlling for other prognostic parameters, a positive margin at the apex is not associated with untoward prognosis.
- Univariate and multivariate analysis of the CaPSURE registry of patients in the United States showed that percentage of biopsies positive for cancer following radical prostatectomy is a significant predictor of both extracapsular disease and disease recurrence.
- A presentation on orthotopic urinary diversion in women requiring cystectomy noted that increase in experience has demonstrated this to be a safe and reliable method of urinary diversion in properly selected patients.
- After reviewing treatment options for ureteral strictures, one presenter concluded that endourologic management of benign ureteral and ureteroenteric strictures provides reasonable first-line therapy. Endoureterotomy has a higher success rate than balloon dilation, and the latter is exceedingly prone to failure for ureteroenteric strictures.
- A presentation regarding the outcome and management of lower pole calculi concluded that for small stones (<10 mm), shockwave lithotripsy is reasonable first-line therapy. For larger stones (>20 mm), percutaneous nephrolithotamy is preferred. For stones intermediate in size (11–20 mm), the main treatment decision is based on renal anatomy and stone composition.
- A review of cost/benefit analyses of the management of male infertility concluded that in cases of severe male factors, such as azoospermia and severe oligospermia, the only treatment approach may be in vitro fertilization or intracytoplasmic sperm injection; but in the more common, treatable forms of male infertility, including vericocele, obstructive azoospermia, endocrine dysfunction, and infection, definitive therapy of these conditions may be more cost-effective.

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